Journal of Neurology, Neurosurgery, and Psychiatry, 1973, **36**, 57–60

Serum measles antibodies in multiple sclerosis

W. CENDROWSKI, I. POLNA, AND K. NIEDZIELSKA

From the Psychoneurological Institute, Pruszków, and the Department of Virology, State Institute of Hygiene, Warsaw, Poland

SUMMARY Serum haemagglutination inhibition/HI/antibody titres to measles virus were examined in 80 multiple sclerosis patients, their 20 sibs, in 990 healthy controls, and 25 control patients. The measles HI titres were significantly raised in the serum of multiple sclerosis patients compared with healthy controls. There was no statistical difference between the levels of HI antibody titres in multiple sclerosis patients and their sibs. The measles HI titres decreased significantly in older age groups of healthy controls, whereas an analogous drop was not found in the multiple sclerosis group. The levels of serum HI antibody titres did not correlate with the sex of patients with multiple sclerosis or the activity of the disease. In the CSF of six multiple sclerosis patients low titres of HI antibodies were detected, whereas none of eight control patients had measurable traces of measles antibodies in the CSF. The significance of these findings in the aetiology of multiple sclerosis is briefly discussed.

Since the report of Adams and Imagawa (1962) who discovered slightly higher antibody titres to measles virus in the sera of patients with multiple sclerosis a number of other studies have been conducted on this subject. Caspary, Chambers, and Field (1969) stated that the role of measles (or indeed other banal viral infections) as 'helper' agents in 'slow' viral infections had yet to be considered and made suggestions as to how ordinary viruses might facilitate the establishment of infection by 'slow viruses'. Isacson (1967) thought that paramyxoviruses, by their mode of replication, might bring out previously hidden antigenic determinants of brain. Another hypothesis assumes the persistence of measles virus in the brains and possibly in the spleens of patients with multiple sclerosis (Panelius, Salmi, Halonen, and Penttinen, 1971).

Whatever is the role of measles virus in the aetiology of multiple sclerosis, the question of raised antibody titres needs further investigation. An attempt therefore was made to examine serum measles antibodies in multiple sclerosis patients, their sibs, in healthy controls, and control patients. Patients with active multiple sclerosis were compared with patients in long remission. In addition, an effort was made to show measurable antibody titres to measles virus in the cerebrospinal fluid of multiple sclerosis patients and control patients.

METHODS

Serum measles antibodies were examined in 80 multiple sclerosis patients aged from 16 to 55 years. The ratio of women to men was 1·1:1. The duration of multiple sclerosis ranged from three months to 25 years. Most of the patients with multiple sclerosis (85%) and all control patients were diagnosed at the Neurological Clinic in Pruszków. The estimations of antibody titres to measles virus were carried out according to four age groups, sex, and the degree of activity of multiple sclerosis. Titres of 1/4 and greater were considered 'positive'. Multiple sclerosis was assessed as active if new relapses or evident progression of the disease occurred during the 12 months period before serological examination.

The group of multiple sclerosis patients was compared with a large group of healthy controls. The latter consisted of 990 subjects, aged from 15 to 50 years, mainly residing in central and western Poland. Another control group consisted of 25 patients with neurological disease other than multiple sclerosis (epilepsy, nine; encephalopathy, three; neurosis, three; sciatica, two; others, eight). Samples of the cerebrospinal fluid were also tested from eight control patients. Eighty serum and seven spinal fluid samples from multiple sclerosis patients and 990

TABLE 1

SERUM MEASLES ANTIBODIES IN PATIENTS WITH MULTIPLE SCLEROSIS, THEIR SIBS, HEALTHY CONTROLS, AND CONTROL PATIENTS

Subjects (no.)	*Age (yr)*	*Positive reactions (no.)*	*Titres*				
			1/4–1/10	1/20–1/40	1/80–1/160	1/164–1/512	≥1/1024
Multiple sclerosis							
4	15–20	4	0	0	3	1	0
17	21–30	16	0	5	7	3	1
30	31–40	29	4	4	11	9	1
29	41–50	28	1	9	8	9	1
Healthy controls							
218	15–20	182	31	79	60	12	0
267	21–30	227	52	127	42	6	0
265	31–40	218	52	121	41	4	0
240	41–50	197	62	112	23	0	0
Sibs							
20	21–55	19	1	9	5	3	1
Control patients							
25	15–50	24	1	12	10	1	0

serum specimens from healthy donors were examined by the haemagglutination inhibition (HI) technique for antibodies to measles virus. This method was described in detail by Clarke and Casals (1958). All sera with high titres of serum HI antibodies were re-examined for measles virus neutralizing antibodies as described by Polna (1971). In all instances fully consistent results were obtained by means of either method. Serum HI measles antibodies were tested twice or three times in eight patients with multiple sclerosis at intervals from three to 10 months.

RESULTS

Measurable serum antibody titres to measles virus were found in 98% of 80 multiple sclerosis patients whereas 990 healthy controls in central and western Poland showed measles antibodies only in 83%. Significantly increased levels of antibody for the multiple sclerosis compared with the control healthy group were recorded for measles virus (Table 1, $\chi^2=48{\cdot}4$; $P<0{\cdot}001$).

Among healthy controls there was gradual drop in antibody titres with age (χ^2 for positive or negative $=51{\cdot}1$; $P<0{\cdot}001$; d.f. $=9$). On the other hand, the titres of HI antibodies in multiple sclerosis patients did not show any correlation with age ($\chi^2=10{\cdot}8$; $P<0{\cdot}70$; d.f. $=12$). Titres ranging above 1/80 were proportionately most frequent in healthy controls at the age 15–20 years and in multiple sclerosis patients at the age 31–40 years. It is noteworthy that only 9·7% of healthy controls had at the age 41–50 years a level of antibodies ranging from 1/80 to 1/160, whereas some patients with multiple sclerosis at this age had titres from 1/512 to 1/2048.

No difference was found in the levels of antibody titres among multiple sclerosis patients and their healthy sibs ($P<0{\cdot}70$). The comparison of antibody titres of multiple sclerosis patients with control patients tended to reach statistical significance, but obviously the control group was too small for this purpose ($0{\cdot}05<P<0{\cdot}10$). Sex did not exert an independent influence on measles antibody titre either in multiple sclerosis patients ($\chi^2=4{\cdot}67$; $P<0{\cdot}50$; d.f. $=4$) or in their sibs ($\chi^2=1{\cdot}18$; $P<0{\cdot}20$; d.f. $=4$) (Table 2).

Patients having active multiple sclerosis were then compared with patients who showed long

TABLE 2

SERUM MEASLES ANTIBODIES ACCORDING TO SEX OF PATIENTS WITH MULTIPLE SCLEROSIS AND THEIR SIBS

Subjects (no.)	*Positive reactions (no.)*	*Sex*	*Titres*				
			1/4–1/10	1/20–1/40	1/80–1/160	1/164–1/512	≥1/1024
Multiple sclerosis							
38	35	M	3	10	15	6	1
42	42	F	2	8	14	16	2
Sibs							
11	11	M	0	7	3	0	1
9	8	F	1	2	2	3	0

TABLE 3

SERUM MEASLES ANTIBODIES IN PATIENTS WITH MULTIPLE SCLEROSIS ACCORDING TO ACTIVITY OF DISEASE

Subjects	(*no.*)	*Titres*				
		1/4–1/10	1/20–1/40	1/80–1/160	1/164–1/512	⩾1/1024
Multiple sclerosis						
Active	59	4	13	24	15	2
Probably active	4	0	2	1	1	0
Inactive	16	1	3	4	6	1

remission. Unfortunately, there were too few patients with inactive multiple sclerosis. The activity of the disease, as was shown in Table 3, was an independent variable and did not correlate with the level of HI measles antibodies in the sera ($\chi^2 = 1{\cdot}56$; $P < 0{\cdot}30$; d.f. = 1).

Among 80 patients with multiple sclerosis there were two affected twins from two dizygotic pairs and nine patients with a familial form of the disease. A female twin with multiple sclerosis had a very high level of HI antibodies (1/512), while the healthy co-twin showed a normal titre. Almost reverse findings were seen in another twin pair. Among nine familial cases, five had increased titre of HI measles antibodies in titres between 1/92 and 1/384.

Serial examinations of serum HI antibodies were very limited. In three patients out of eight with multiple sclerosis, increased titres became normal within 10 months and in the remaining five they were unchanged.

It is noteworthy that in the cerebrospinal fluid (CSF) of six multiple sclerosis patients low titres of HI antibodies were detected and ranged from 1/4 to 1/16. None of eight controls had a measurable amount of HI measles antibodies in the CSF. It is important that the level of CSF antibodies in multiple sclerosis showed no correlation with that of serum.

Although the method used was proved to be sensitive, it was of interest to examine sera of patients with other infectious diseases of the brain. A child with measles encephalitis had high titre (1/384). Two adult patients with encephalomyelitis of unknown aetiology showed normal titres.

DISCUSSION

The results of this study provide distinct confirmation of the earlier observations indicating increased levels of HI antibody titres to measles virus in patients with multiple sclerosis compared with healthy controls matched for age (Henson, Brody, Sever, Dyken, and Cannon, 1970). However, measles is endemic in the general population in which these studies were carried out and the fact that almost all multiple sclerosis patients showed detectable measles antibodies has little significance. Panelius (1969) tried to establish a correlation between more frequent occurrence of multiple sclerosis in southern Finland and higher titres of measles antibodies. This relationship is not certain. Increased level of antibody titres was found both in Minneapolis with a high prevalence rate (6·4/10,000) and in Washington D.C. (2·7/10,000) where the disease is less common (Sever, Kurtzke, Alter, and Schumacher, 1971). No correlation was also shown between the frequency of measles infection in childhood and the occurrence of multiple sclerosis (Lenman, Brodie, and Peters, 1969).

Analysis without correcting for age revealed that levels of HI antibodies in multiple sclerosis patients and their sibs were similar. Yet this point of comparison is controversial, because Panelius, Salmi, Halonen, Kivalo, Rinne, and Penttinen (1972) found a weak statistical difference between multiple sclerosis patients and their sibs ($P = 0{\cdot}05$). More important from the aetiological point of view is that there is limited correlation between the frequency rate of multiple sclerosis among relatives of patients and the grade of kinship (Cendrowski, 1968). The disease appeared to be more common among co-twins and sibs than among parents and cousins. There seems to be a positive relationship between higher frequency of multiple sclerosis among sibs and increased titres of HI measles antibodies in this group of relatives.

The absence of gradual decline of antibody titres related to age in the multiple sclerosis group may be caused by different factors. One of them seems to be the nature of serum measles

antibodies in multiple sclerosis. The latter are of 7S type, whereas in healthy controls they are of 19S type (Schluederberg, 1965).

A further point of the analysis is the relationship between the age at onset and the activity of multiple sclerosis on the one hand and the level of HI antibody titres to measles on the other. Henson *et al.* (1970) considered that there was a slight tendency for those with recent onset to have higher HI antibody titres to measles but this was not statistically proved. The activity of multiple sclerosis had no apparent influence on the level of HI antibody titres. Unfortunately, this means little because there is no correlation between HI antibodies and gel precipitation antibodies to measles virus (Panelius *et al.*, 1971). It is therefore possible that some of the patients with early onset or active multiple sclerosis may have increased gel precipitation antibodies. In addition, an increased level of serum antibodies is found also in different autoimmune diseases (Lucas, Brouwer, Feltkamp, Veen, and Loghem, 1972). Recent serological investigation indicates that measles virus may cause in patients with multiple sclerosis a population of various antibodies which are not related to each other. Some multiple sclerosis patients demonstrate characteristic components of gel precipitation antibodies which are similar to or identical with those of patients with subacute sclerosing panencephalitis (Panelius *et al.*, 1971). This study shows that the occurrence of HI measles antibodies in the CSF, as well as long duration of measles antibodies in the sera, may suggest the persistence of measles virus in some multiple sclerosis patients. These findings are not yet conclusive. Isolation of measles virus from brain biopsy in active multiple sclerosis would furnish more convincing proof of viral aetiology of the disease.

REFERENCES

Adams, J. M., and Imagawa, D. T. (1962). Measles antibodies in multiple sclerosis. *Proceedings of the Society for Experimental and Biological Medicine*, **111**, 562–566.

Caspary, E. A., Chambers, M. E., and Field, E. J. (1969). Antibodies to measles antigen, control antigen, and monkey kidney antigen. *Neurology (Minneap.)*, **19**, 1038–1042.

Cendrowski, W. S. (1968). Multiple sclerosis: discordance in three pairs of dizygotic twins. *Journal of Medical Genetics*, **5**, 266–268.

Clarke, D. H., and Casals, J. (1958). Techniques for hemagglutination and hemagglutination-inhibition with arthropod-borne viruses. *American Journal of Tropical Medicine and Hygiene*, **7**, 561–573.

Henson, T. E., Brody, J. A., Sever, J. L., Dyken, M. L., and Cannon, J. (1970). Measles antibody titers in multiple sclerosis patients, siblings, and controls. *Journal of the American Medical Association*, **211**, 1985–1988.

Isacson, P. (1967). Myxoviruses and autoimmunity. *Progress in Allergy*, **10**, 256–292.

Lenman, J. A. R., and Peters, T. J. (1969). Herpes zoster and multiple sclerosis. *British Medical Journal*, **2**, 218–220.

Lucas, C. J., Brouwer, R., Feltkamp, T. E. W., Veen, J. H. Ten, and Loghem, J. J. van (1972). Measles antibodies in sera from patients with autoimmune diseases. *Lancet*, **1**, 115–116.

Panelius, M. (1969). Studies on epidemiological, clinical, and etiological aspects of multiple sclerosis. *Acta Neurologica Scandinavica*, Suppl., **39**, 1–82.

Panelius, M., Salmi, A., Halonen, P., and Penttinen, K. (1971). Measles antibodies detected with various techniques in sera of patients with multiple sclerosis, *Acta Neurologica Scandinavica*, **47**, 315–330.

Panelius, M., Salmi, A., Halonen, P., Kivalo, E., Rinne, U., and Penttinen, K. (1972). Virus antibodies in sera of patients with multiple sclerosis, in controls matched for age, sex, and place of residence, and in siblings. *Multiple Sclerosis. N. Holland Publ. Amsterdam*, 1972, pp. 3–6.

Schluederberg, A. (1965). Modification of immune response by previous experience with measles, *Archiv für die gesamte Virusforschung*, **16**, 347–350.

Sever, J. L., Kurtzke, J. F., Alter, M., Schumacher, G. A., Gilkeson, M. R., Ellenberg, J. H., and Brody, J. A. (1971). Virus antibodies and multiple sclerosis, *Archives of Neurology (Chicago)*, **24**, 489–494.

ADDENDUM

Since the printing of the manuscript two more papers have come to the attention of one of us (W.S.C.). J. Millar and his colleagues (Symposium on Multiple Sclerosis, Gothenburg, 7–9 September 1972) more frequently found measles antibody in oligoclonal IgG from multiple sclerosis CSF than they did in control CSF. E. Field and his colleagues (*Lancet*, 1972, **2**, 280) identified 'inclusion tubules' similar to measles virus within astroglial cells in a biopsy specimen of multiple sclerosis brain.